Background: Sustained virological response (SVR) rates in previous non-responders to pegylated interferon (PEG-IFN)-α and ribavirin for chronic HCV remain low (~10%). We hypothesize that continuous subcutaneous delivery of fully potent interferon (IFN)-α2b via an external pump will lead to stable blood concentrations and thereby prevent subtherapeutic trough levels associated with viral breakthrough. The aims of the study were to assess safety, tolerability and virological response in patients who were previous PEG-IFN-α/ribavirin non-responders.

Methods: We randomized 30 HCV genotype 1 (n=24) and genotype 4 (n=6) patients to receive 6, 9 or 12 million units (MU) IFN-α2b daily by continuous subcutaneous administration using an insulin pump (MiniMed® 508; Medtronic Inc., Minneapolis, MN, USA) in combination with ribavirin (1,000–1,600 mg) for 48 weeks.

Results: The magnitude of viral decline in the 12 MU group after 4 weeks of treatment was 2.67 log HCV RNA compared with 1.21 and 1.27 log HCV RNA in the 9 and 6 MU groups, respectively (P=0.001). In the intention-to-treat analysis, the SVR rate was 20% (6/30). The per-protocol SVR rate was 25% (6/24), of which four out of six patients in the high-dose arm achieved SVR. Adverse events appeared dose-dependent, were mostly mild-to-moderate and were typical of IFN therapy. Five patients developed irritation and/or abscesses at the injection site. Six serious adverse events were reported in five patients.

Conclusions: Continuous delivery of IFN-α2b can induce a strong dose-dependent viral suppression. This could be an effective approach in conjunction with, or as lead-in therapy prior to, treatment with a direct antiviral agent.

Original article

Continuous interferon-α2b infusion in combination with ribavirin for chronic hepatitis C in treatment-experienced patients

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Introduction

Chronic HCV infection is one of the leading causes of cirrhosis, hepatocellular carcinoma and end-stage liver disease [1]. The current standard care for chronic HCV infection is a 24-week or 48-week regimen with pegylated interferon (PEG-IFN)-α and ribavirin (RBV). This treatment regimen leads to sustained viral responses in 42–82% of patients depending on host factors and viral genotype [2–4]. Unfortunately, 50–60% of patients with genotypes 1 and 4 do not respond to this treatment regimen, which has led to a continuous increase in the pool of patients non-responsive to this treatment regimen. Retreatment sustained virological response (SVR) rates of these patients range between 4% and 15%. Increasing this percentage is considered to be a great challenge [5–10].

Pegylation of interferon (IFN)-α has improved the pharmacokinetic profile of conventional IFN by maintaining constant blood levels. This enabled once-weekly dosing and resulted in higher response rates. However, it has been shown that the volume of distribution owing to pegylation is considerably restricted, decreasing biological activity and potentially decreasing treatment efficacy [11]. Continuous exposure to IFN-α could potentially overcome this hindrance by providing
sustained and constant levels of a fully potent protein. We hypothesize that constant levels could induce a stable viral suppression and prevent side effects associated with peaks after injection as well as subtherapeutic drug levels associated with troughs.

The continuous infusion of IFN-α has been studied in several small Phase I studies. A significant decrease in serum alanine aminotransferase was observed in one study and continuous infusion of IFN was safe and well-tolerated. However, these studies were small and the treatment length was inadequate [12–14].

In this pilot study we aimed to investigate efficacy, safety and feasibility of continuous subcutaneous infusion of IFN-α2b in combination with weight-based RBV (15.2 mg/kg) for 48 weeks in patients who previously failed to respond to PEG-IFN-α and RBV.

Methods

This study, referred to as the SCIN-C study (Subcutaneous Continuous Interferon-α2b infusion in Chronic Hepatitis C Previous Nonresponders), was an investigator-initiated study, sponsored by the Foundation of Liver and Gastrointestinal Disorders (SLO, Rotterdam, the Netherlands). Financial support and infusion devices were obtained from Medtronic Inc. (Minneapolis, MN, USA).

Study design

The study was a single-centre, randomized, open-label, dose-finding study with three treatment arms. We randomly assigned 24 genotype 1 and six genotype 4 patients in a 1:1:1 ratio to receive 6, 9 or 12 million units (MU) IFN-α2b per day by continuous subcutaneous infusion in combination with daily RBV (Figure 1). Stratified random assignment was used to balance the genotype distribution. RBV dosage was weight-based: 1,000 mg for patients ≤65 kg, 1,200 mg for patients 65–80 kg, 1,400 mg for patients >80–100 kg and 1,600 mg for patients >100 kg. Patients visited the outpatient clinic at time of screening, at baseline, during treatment (weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48) and during post-treatment follow-up (weeks 52, 60 and 72). In the event of grade 3 adverse events the IFN-α2b dose was reduced by 1.5 MU/day. In the case of absolute neutrophil count <750 cells/μl or platelet count <50,000 platelets/μl, the IFN-α2b dose was reduced to 75% of the initial dose. This dose reduction was not performed in the first 12 weeks of therapy or in cases of HCV RNA positivity after 12 weeks of therapy, considering the negative effect of dose reductions on virological response. In cases of absolute neutrophil count <375 cells/μl or platelet count <25,000 platelets/μl the IFN-α2b dose was reduced to 50% of the initial dose regardless of...
viral load or duration of therapy. When the haemoglobin concentration dropped below 5.0 mmol/l the IFN-α2b dose was reduced to 75%; in cases of a drop below 4.0 mmol/l the RBV dose was reduced to 10 mg/kg daily and patients were treated with blood transfusions.

Patients
Patients were considered eligible for enrolment in this study if they were between 18 and 60 years of age, had chronic hepatitis C infection genotype 1 or 4, were unresponsive to previous PEG-IFN/RBV therapy and had persistently increased serum alanine aminotransferase or histological evidence of continuing or progressive fibrosis. Non-response to previous therapy was defined as null response (a less than 2 log drop at week 12 during previous therapy), partial response (HCV RNA positivity at week 24), breakthrough (viral breakthrough during therapy) or relapse (viral relapse after therapy). Duration of previous treatment was required to be at least 3 months. All patients had detectable HCV RNA by a PCR assay. Patients were excluded if they had signs of decompensated liver disease, evidence of hepatocellular carcinoma (hepatic imaging performed within 3 months prior to screening), other acquired or inherited liver diseases, coinfection with HIV or chronic hepatitis B, significant pulmonary, cardiovascular or renal dysfunction, malignancies in the previous 5 years, history of seizure disorder, uncontrolled thyroid disease, psychiatric disorders, the presence of immunological disorders, pregnancy, breastfeeding and/or active substance abuse (intravenous drugs or >80 g/day alcohol).

Continuous subcutaneous infusion of interferon-α2b
For subcutaneous infusion of IFN-α2b the MiniMed® insulin pump (Medtronic Inc.) was used. At the time of screening, patients received instructions regarding pump handling and operation. At baseline these instructions were repeated and patients were asked to demonstrate how to handle the MiniMed® pump. If patients encountered problems during treatment regarding pump handling, they were instructed to call one of the investigators. Patients received five reservoirs with IFN-α2b for every 2 weeks on therapy. Reservoirs were replaced every 3 days.

Assessment of safety and feasibility
Safety was assessed by physical examination, laboratory tests and recording of adverse events at every visit during and after therapy. At every outpatient clinic visit patients were asked if any problems regarding to pump handling had occurred. Furthermore, the daily IFN-α2b dose administration was checked using an automated dosing registry within the pump and patients registered the daily IFN dose and RBV dose on drug accountability forms.

Assessment of virological response
HCV RNA was measured at every visit from baseline until week 12, at weeks 24, 36 and 48 and at every visit during follow-up using the VERSANT® HCV RNA 3.0 quantitative assay (Siemens Medical Solutions, Eindhoven, the Netherlands; branched DNA, lower limit of quantification 615 IU/ml). In cases of unquantifiable HCV RNA a qualitative assay (TaqMan HCV test version 1.0; Cobas Amplicor/Cobas TaqMan, Roche Diagnostics, Almere, the Netherlands; lower limit of detection <15 IU/ml) was used for the detection of HCV RNA. Treatment was discontinued in patients with detectable HCV RNA at week 24. Virological end points were viral decline during therapy and HCV RNA negativity at week 48 and after 24 weeks of follow-up.

Interferon level determination
IFN-α2b concentrations were determined by application of a quantitative sandwich ELISA method (BMS216INST; Bender Medsystems Diagnostics GmbH, Vienna, Austria).

Interleukin-28B genotype determination
The interleukin (IL) 28b single nucleotide polymorphism (SNP) rs12979860 variants were determined using competitive allele-specific PCR (KASP; KBioscience, Hoddesdon, UK).

Statistical analysis
Fisher’s exact and χ² tests were used to compare adverse events and virological responses between different treatment arms. Both parametric and non-parametric tests were performed to compare continuous variables. Linear regression was used to analyse viral decline and virological responses during treatment. Continuous variables are expressed as means ±SD or medians (range) where appropriate. All statistical tests were two-sided and P<0.05 was considered to be statistically significant. SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analysis.

Results
Patients
Patients were enrolled between July 2007 and November 2008. A total of 32 patients were assessed for eligibility and 30 patients were randomly assigned to one of three treatment arms (Figure 1). End of follow-up data are available in 26 patients (87%; Figure 2). Baseline characteristics of patients are summarized in Table 1. No significant differences between treatment arms were observed. Patients were predominantly Caucasian (93%) and were infected with HCV genotype 1 (80%). A total of 20 patients were classified as null or partial responders during previous therapy and 10 patients...
experienced viral breakthrough during or viral relapse after their previous treatment. IL28B SNP rs12979860 was determined in 29 patients. As expected, most patients had the intermediate or poor response variants CT and TT, and only three patients had the favourable genotype CC. No significant differences between the three treatment arms were found.

Safety and tolerability
Adverse events, haematological abnormalities, dose reductions and treatment discontinuations are listed in Table 2. All patients had at least one adverse event. In the 12 MU group, 5.8% of adverse events were classified as severe compared with 3.3% and 2.2% of adverse events in the 9 and 6 MU groups, respectively ($P=0.230$). A total of 24 infections occurred in 17 patients. Injection-site reactions occurred in 21 patients. Four of these reactions were defined as small skin abscesses at the injection site, all of which improved rapidly after drainage. Severe injection-site reactions mostly occurred in the first months of this study probably because of less experience regarding replacement of the infusion sets. In five patients, injection-site reactions were defined as severe and in two patients as a serious adverse event (SAE) because of hospital admission. One of these two hospitalized patients was diagnosed with cellulitis and antiviral treatment was discontinued temporarily. Some weeks later, this patient developed a hyperglycaemia-induced seizure, the patient’s second SAE, and treatment was discontinued permanently. This patient suffered from diabetes mellitus and had not been compliant with insulin therapy. Other SAEs included community-acquired pneumonia, diarrhoea and an upper respiratory tract infection. In total six SAEs occurred in five
patients: four patients in the 12 MU and one patient in the 9 MU group (P=0.027). All SAEs resolved after temporary or permanent discontinuation of treatment. Four out of five patients with SAEs had cirrhosis. Dose reductions owing to haematological abnormalities or adverse events were performed in 5 out of 30 patients (17%): 3 patients from the 12 MU group and 2 patients from the 9 MU group. In six patients, treatment was discontinued prematurely: four patients from the 12 MU group and two patients from the 12 MU group (P=0.12). Reasons for discontinuation were the occurrence of an SAE in three patients, withdrawal of consent in two patients and incarceration in one patient.

Interferon levels
IFN levels increased dose dependently, reaching peak levels between 48 h and 1 week of treatment followed by continuous steady-state levels during the remaining treatment period. Mean IFN levels at week 4 were 344 pg/ml, 264 pg/ml and 225 pg/ml in the 12, 9 and 6 MU groups, respectively. Between patients a great interindividual variability was observed. A weak negative correlation was found between IFN levels and viral load (r=-0.297, P<0.001).

Viral kinetics
The magnitude of viral decline in the 12 MU group after 4 weeks of treatment was 2.67 log HCV RNA compared with 1.21 and 1.27 log HCV RNA in the 9 and 6 MU groups, respectively (P=0.001; Figure 3). After 12 weeks viral decline was 3.57 log HCV RNA in the 12 MU group compared with 2.8 log HCV RNA in the 9 MU group and 1.91 log HCV RNA in the 6 MU group (P=0.075). In the multivariate linear regression analysis, IFN-α2b dose (P=0.004) and the IL28b variant (P=0.017) were significantly associated with viral decline at week 4.

Viral response
In the intention-to-treat analysis 6 out of 30 (20%) patients achieved SVR. Three out of 20 (15%) previous null or partial responders (one from the 9 MU group and two from the 12 MU group) achieved SVR. The remaining 3 patients who achieved SVR were patients with a viral breakthrough during, or relapse after, previous antiviral therapy (1 from the 6 MU group and 2 from the 12 MU group). Of the 6 SVR patients 3 had cirrhosis (all from the 12 MU group). Five out of 24 (21%) genotype 1 patients and 1 out of 6 (17%) genotype 4 patients achieved SVR.

In the per-protocol analysis the SVR rate was 6 out of 24 (25%). Of the 6 patients (67%) treated per protocol in the 12 MU group, 4 achieved SVR compared with 1 out of 10 (10%) and 1 out of 8 (12.5%) in the 6 and 9 MU groups, respectively (P=0.042).

Virological response rates are shown in Figure 4. At week 4, one patient (from the 6 MU group) had undetectable HCV RNA. In the 12, 9 and 6 MU groups,
respectively, 4, 2 and 2 patients had undetectable HCV RNA at week 12 ($P=0.384$). Eight out of 10 patients from the 12 MU group became HCV-RNA-negative during therapy compared with 5 out of 10 (50%) and 2 out of 10 (20%) in the 9 and 6 MU groups, respectively ($P=0.027$). Two of these patients were HCV-negative before week 24 (weeks 8 and 12) but had to stop treatment because of an SAE. Importantly, 10 out of 20 patients with a previous null or partial response to antiviral therapy became HCV-RNA-negative ($HCV\text{ RNA}<15\text{ IU/ml}$).

All patients with the IL28B rs12979860 CC variant became HCV-RNA-negative, whereas only 50% of patients with the CT (10/20) and TT variants (3/6) became HCV-RNA-negative ($P=0.423$). In patients who achieved SVR, the IL28B rs12979860 variant was CC in 2 patients (1 in each of the 6 and 9 MU groups) and CT in 4 patients (all from the 12 MU group). The third CC patient had a complete early virological response; however, treatment was stopped in this patient in week 21 because of an SAE. In the 12 MU group, virological responses were independent of IL28B genotype.

None of the patients who had less than a 2 log decline of HCV RNA at week 4 achieved SVR and thus the negative predictive value was 100%. Thirteen out of 27 (48%) patients had detectable HCV RNA at week 12 of antiviral therapy and none of these patients achieved an SVR (negative predictive value 100%).

### Table 2. Dose reductions, discontinuations, adverse events and laboratory abnormalities

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=30)</th>
<th>12 MU (n=10)</th>
<th>9 MU (n=10)</th>
<th>6 MU (n=10)</th>
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<td>8</td>
<td>3</td>
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<td>Loss of appetite</td>
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<td>5</td>
<td>6</td>
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<td>6</td>
<td>6</td>
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<tr>
<td>Injection-site reaction</td>
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<td>5</td>
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<tr>
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<td>4</td>
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<tr>
<td>Alopecia</td>
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<td>Depression</td>
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<td>4</td>
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*Defined as haemoglobin <6.2 mmol/l. °Defined as absolute neutrophil count <750 cells/μl. †Defined as platelet count <50,000 platelets/μl. MU, million units.
Discussion

This pilot study is the first to investigate safety and efficacy of continuous infusion of high daily doses of IFN-α2b in combination with RBV for a full 48 weeks in chronic hepatitis C patients who previously failed therapy. The rationale of continuous subcutaneous infusion of IFN-α2b was firstly to optimize response by maintaining constant high IFN-α blood concentrations enabling continuous viral suppression and secondly prevention of side effects associated with IFN peaks, which can occur with weekly injections of PEG-IFN-α.

Our most important finding was that delivery of IFN-α2b in combination with RBV resulted in a strong dose-dependent viral suppression. At week 4, two-thirds of patients from the 12 MU group had unquantifiable HCV RNA and at week 12 all patients from this group had unquantifiable HCV RNA. Furthermore, 50% of previous null and partial responders became HCV-RNA-negative during treatment. Six out of 30 (20%) patients achieved SVR. The per-protocol SVR rate was 25% with 4 out of 6 (67%) patients from the 12 MU group achieving SVR.

This strong viral suppression of high-dose continuous subcutaneous IFN-α2b infusion could play an important role within the recently proposed concept of lead-in therapy prior to triple therapy with PEG-IFN-α, RBV and a direct antiviral agent. In these studies investigating direct antiviral agents, a rapid virological decline during a PEG-IFN-α/RBV lead-in was crucial to achieve SVR and prevent virological breakthrough or relapse [15–18]. Short-term high-dose continuous IFN-α infusion could help to achieve this necessary rapid viral decline and therefore this concept of continuous IFN-α2b could play an important role in the new era of direct antiviral agents. In particular, patients with a known null or partial response to previous therapy with PEG-IFN-α and RBV could benefit from this treatment concept.

In addition, this study reports on the predictiveness of SNPs near the IL28B gene in previous non-responders. As expected, most patients had the rs12979860 CT and TT variants that are associated with decreased responsiveness to PEG-IFN/RBV therapy, whereas only three patients had the favourable CC variant of this SNP. An important finding was that the strong viral suppression in patients treated with 12 MU of IFN-α2b was independent of IL28b genotype. These results suggest that the lack of innate IFN responsiveness seen in this group of patients can be overcome by high doses of continuous IFN-α2b infusion. Patients with the CC genotype had a more pronounced virological response compared with CT and TT patients. Response rates between patients with CT and TT variants were comparable.

Side effects were typically IFN-related and severity increased as dose increased. Weekly peaks of side effects did not occur; however, intensity of side effects appeared comparable with treatment with PEG-IFN-α and RBV.

Figure 3. Virological responses during therapy per treatment arm

Figure 4. Viral decline during therapy

Rapid virological response (RVR) was defined as HCV RNA<15 IU/ml at week 4. Partial early virological response (pEVR) was defined as >2 log drop of HCV RNA at week 12. Complete early virological response (EVR) was defined as HCV RNA<15 IU/ml at week 12. Virological response (VR) at week 24 was defined as HCV RNA<15 IU/ml at end of treatment. Sustained virological response (SVR) was defined as HCV RNA<15 IU/ml at 24 weeks after treatment discontinuation. MU, million units.

The magnitude of viral decline in the 12 million units (MU) group after 4 weeks of treatment was 2.67 log HCV RNA compared with 1.21 and 1.27 log HCV RNA in the 9 and 6 MU groups, respectively (P=0.001).
Five patients developed skin abscesses and severe injection-site reactions. These reactions occurred only in the early phase of the study and could be prevented later on in the study by adequate instructions for replacement of the injection cannula (infusion sets). Most SAEs occurred in cirrhotic patients, for this reason caution is warranted in this patient group. To prevent infectious complications antibiotic prophylactic therapy should be considered. Dose reductions and discontinuation occurred only in the 9 and 12 MU groups. The most common reasons for dose reductions were adverse events and haematological abnormalities.

IFN levels were measured throughout the study; all patients reached steady-state levels in the first weeks of treatment. The pharmacokinetic profile of continuous infusion of IFN-α differs from that of treatment with PEG-IFN-α2a or PEG-IFN-α2b and RBV, which causes peak and trough concentrations. A study investigating pharmacokinetics of PEG-IFN-α2a and PEG-IFN-α2b showed that undetectable trough concentrations of PEG-IFN-α2b can occur in some patients [19]. This phenomenon did not occur in our study.

A great interindividual variability of IFN-α concentrations exists between patients. For this reason it is difficult to use these concentrations for prediction of treatment outcome. To our knowledge, to date, no data have been published on the predictiveness of (PEG)IFN-α concentrations on treatment outcome.

Approximately 50–60% of genotype 1 patients are non-responsive to treatment with PEG-IFN-α and RBV for chronic hepatitis C. Several treatment options to cure these difficult-to-treat patients have been investigated. Retreatment of genotype 1 patients who previously failed PEG-IFN-α and RBV therapy with PEG-IFN-α2b and weight-based RBV lead to SVR rates up to 11% [8]. Comparable SVR rates were achieved with retreatment of true non-responders with consensus IFN and RBV [5]. Studies investigating PEG-IFN induction therapy could not demonstrate an increase in SVR rates. However, early virological response rates were increased in patients receiving induction therapy [6,7,9,10]. The highest SVR rates were achieved when combining a PEG-IFN-α2a/RBV induction regimen with an extension of the treatment duration to 72 weeks [7]. A total of 16% of these patients, who were non-responsive to previous therapy with PEG-IFN-α and RBV, achieved SVR.

In our study, treatment with IFN-α2b and RBV by continuous infusion led to an intention-to-treat SVR rate of 20%, which was nearly twice as high compared with the SVR rate of retreatment with PEG-IFN-α and RBV reported so far [8]. A limitation of this study is the lack of a control arm. However, retreating previous null or partial responders to PEG-IFN and RBV with the same regimen will have limited chances of SVR.

In conclusion, continuous delivery of high doses of IFN-α2b with a pump device can be carried out successfully in this difficult-to-treat population. If side effects are managed adequately, continuous delivery of IFN-α2b can induce a strong dose-dependent viral suppression leading to improved SVR rates. Short-term continuous IFN treatment could also be an effective approach in conjunction with or as lead-in therapy prior to treatment with a direct antiviral agent, especially in difficult-to-treat populations.

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Disclosure statement

The authors declare no competing interests.

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